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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/836,410 | Applicant(s) GENDRON ET AL. | |
|---|---|---|---|
| | Examiner Karen Lacourciere | Art Unit 1635 | |

*– Th MAILING DATE of this communication appears on the cover sheet with the correspondence address –*

**Period f r Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-49 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) 1 is/are allowed.

6)☒ Claim(s) 2-49 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

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## DETAILED ACTION

### *Information Disclosure Statement*

Reference number 1, Sambrook et al., on PTO form 1449, filed 04-17-01, was not considered because the reference was not provided.

### *Oath/Declaration*

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

The citizenship of inventor Paradis has been altered on the declaration, but this alteration has not been initialed.

### *Claim Objections*

Claim 9 is objected to because of the following informalities: The word "complementarity" in line 4 of the claim should be corrected to read "complementary". Appropriate correction is required.

Claim 12 is objected to because of the following informalities: The word "complementarity" in line 3 of the claim should be corrected to read "complementary". Appropriate correction is required.

Claim 16 is objected to because of the following informalities: The word "complementarity" in line 2 of the claim should be corrected to read "complementary". Appropriate correction is required.

Claim 41 is objected to because of the following informalities: The word "complementarity" in line 3 of the claim should be corrected to read "complementary". Additionally, the phrase "is of at least" is not proper English. Appropriate correction is required.

Claim 44 is objected to because of the following informalities: The word "complementarity" in line 2 of the claim should be corrected to read "complementary". Additionally, the phrase "is of at least" is not proper English. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 6-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is indefinite due to the recitation "antisense cDNA". It is unclear whether the claimed molecule is a doublestranded cDNA, expressing an antisense consisting of SEQ ID NO: 3, as implied by the term cDNA, or if the claimed molecule is an antisense molecule consisting of SEQ ID NO: 3.

Claim 7 is indefinite due to the recitation "antisense cDNA". It is unclear whether the claimed molecule is a doublestranded cDNA, expressing an antisense consisting of SEQ ID NO: 4, as implied by the term cDNA, or if the claimed molecule is an antisense molecule consisting of SEQ ID NO: 4.

Claim 8 is indefinite due to the recitation "derived from". The metes and bounds of the term "derived from" are unclear, for example, what types of changes and what degree of changes can occur in a molecule to be considered to be "derived from" SEQ ID NO: 2, rather than being an entirely different cDNA. Claims 9, 10 and 36-40 are indefinite for the same reasons due to their dependence on claim 8.

Claim 9 is indefinite due to the recitation "low and high stringency conditions". The term "low and high stringency" in claim 9 is a relative term that renders the claim indefinite. The term "low and high stringency" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Claims 10 and 36-40 are indefinite for the same reasons due to dependence on claim 9.

Claim 11 is indefinite due to the recitation "effective amount", because the claim does not recite what the effect of the composition is. One skilled in the art would not know what amount of the antisense molecule is an "effective amount" because there is nothing to determine what effect is required. Claims 12-14 are indefinite for the same reasons due to their dependence on claim 11.

Claim 11 is indefinite due to the recitation "derived from". The metes and bounds of the term "derived from" are unclear, for example, what types of changes and what degree of changes can occur in a molecule to be considered to be "derived from" SEQ ID NO: 2, rather than being an entirely different cDNA. Claims 12-14 are indefinite for the same reasons due to their dependence on claim 11.

Claim 13 is indefinite due to the recitation "low and high stringency conditions". The term "low and high stringency" in claim 13 is a relative term that renders the claim indefinite. The term "low and high stringency" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 15 is indefinite due to the recitation "derived from". The metes and bounds of the term "derived from" are unclear, for example, what types of changes and what degree of changes can occur in a molecule to be considered to be "derived from" SEQ ID NO: 2, rather than being an entirely different cDNA. Claims 16-21 are indefinite for the same reasons due to dependence on claim 15.

Claim 15 is indefinite due to the recitation "excess of a tubedown-1 gene". The term "excess of a tubedown-1 gene" in claim 15 is a relative term that renders the claim indefinite. The term "excess of a tubedown-1 gene" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. This phrase is further indefinite because it is unclear how cells would produce an excess of the gene, rather than an excess of mRNA or protein, which is produced from the gene; cells normally do not produce a gene. Claims 16-21 are indefinite for the same reasons due to dependence on claim 15.

Claim 15 is indefinite due to the recitation "biologically active". It is unclear what activities are encompassed in the term "biologically active". Claims 16-21 are indefinite for the same reasons due to dependence on claim 15.

Claim 17 is indefinite due to the recitation "low and high stringency conditions". The term "low and high stringency" in claim 17 is a relative term that renders the claim indefinite. The term "low and high stringency" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Claims 18-21 are indefinite for the same reasons due to dependence on claim 17.

Claim 20 is indefinite because it recites a Markush group, but the language of the claims seems to recite only one member of the Markush group "a lentivirus, adenovirus, adeno-associated virus and virus-like vectors." To be clear, the claims should be amended to clarify that each of the members of the Markush group are individual vectors, for example, this rejection would be obviated if the phrase were amended to read "a lentvirus vector, an adenovirus vector, an adeno-associated virus vector and a virus-like vector."

Claim 20 is indefinite due to the recitation "virus-like vectors". It is unclear what vectors would be encompassed in the term "virus-like vectors", for example, what characteristics would a vector need to be considered "like" a virus vector.

Claim 22 recites the limitation "said condition" in lines 3-4 of the claim. There is insufficient antecedent basis for this limitation in the claim. Claims 23-27 are indefinite for the same reasons due to dependence on claim 22

Claim 22 is indefinite due to the recitation "derived from". The metes and bounds of the term "derived from" are unclear, for example, what types of changes and what degree of changes can occur in a molecule to be considered to be "derived from" SEQ ID NO: 2, rather than being an entirely different cDNA. Claims 23-27 are indefinite for the same reasons due to dependence on claim 22.

Claim 24 is indefinite because it is unclear what step claim 24 adds to the method of claim 23, because claim 23 seems to require that the antisense cDNA is generated ex vivo, and then administered to the mammal. It is unclear if claim 24 requires a second cDNA to be generated and administered to the cell or if it is clarifying the method of making the cDNA administered in claim 23, which seems to be inherent to the method of claim 23 and, therefore, claim 24 would not further limit claim 23. Claim 25 is indefinite for the same reasons due to dependence on claim 24.

Claim 25 is indefinite because the antecedent basis for "the antisense cDNA's" is unclear because it is unclear whether the method of claim 24 uses multiple cDNA's.

Claim 25 is further indefinite because it is unclear how the antisense can be phosphoramidate, phosphorothioate, methylphosphonate and other modified analogs. For example, do the cDNA's comprise backbone modifications of each type, or do the cDNA's comprise all of one type of backbone modification and, if so, are all linkages

required to be a particular type or do the claimed cDNA's comprise at least one of the recited linkages.

Claim 25 is indefinite because the scope of "other modified analogs of said cDNA". It is unclear what "analogs" would encompass, for example, what types of modifications and what degree of changes can be made to a molecule an have that molecule be considered an analog of the cDNA, rather than a different molecule, for example, does analog include base changes and, if so, how many base changes can be made in the cDNA and still be considered an analog?

Claim 25 recites the limitation "said cDNA" in line two of the claim. There is insufficient antecedent basis for this limitation in the claim. The antecedent basis is unclear because in line one claim 25 recites more than one cDNA.

Claim 26 is indefinite because it is unclear how the method of claim 26 and 23 are related, for example, is the individual recited in claim 26 the mammal recited in claim 23, or are antisense cDNA's administered to two different individuals/mammals. It is unclear if claim 26 is limiting the method of administration of claim 23 or if it is an entirely separate method. Claim 27 is indefinite for the same reasons due to dependence on claim 26.

Claim 28 is indefinite due to the recitation "derived from". The metes and bounds of the term "derived from" are unclear, for example, what types of changes and what degree of changes can occur in a molecule to be considered to be "derived from" SEQ ID NO: 2, rather than being an entirely different cDNA. Claims 29-33 are indefinite for the same reasons due to dependence on claim 28.

Claim 28 recites the limitation "said condition" in line 4 of the claim. There is insufficient antecedent basis for this limitation in the claim. Claims 29-33 are indefinite for the same reasons due to dependence on claim 28.

Claim 30 is indefinite because it is unclear what step claim 30 adds to the methods of claims 28 and 29, because claims 28 and 29 seem to require that the antisense cDNA is generated ex vivo, and then administered to the mammal. It is unclear if claim 30 requires a second cDNA to be generated and administered to the cell or if it is clarifying the method of making the cDNA administered in claims 28 and 29, which seems to be inherent to the methods of claims 28 and 29 and, therefore, claim 30 would not further limit claims 28 and 29. Claim 31 is indefinite for the same reasons due to dependence on claim 30.

Claim 30 recites the limitation "the antisense oligonucleotide" in lines 1-2 of the claim. There is insufficient antecedent basis for this limitation in the claim. Claim 31 is indefinite for the same reasons due to dependence on claim 30.

Claim 31 is indefinite because the antecedent basis for "the antisense cDNA molecules" is unclear because it is unclear whether the method of claim 30 uses multiple cDNA molecules.

Claim 31 is further indefinite because it is unclear how the antisense can be phosphoramidate, phosphorothioate, methylphosphonate and other modified analogs. For example, do the cDNA molecules comprise backbone modifications of each type, or do the cDNA molecules comprise all of one type of backbone modification and, if so, are

all linkages required to be a particular type or do the claimed cDNA molecules comprise at least one of the recited linkages.

Claim 31 is indefinite because the scope of "other modified analogs of said cDNA molecules". It is unclear what "analogs" would encompass, for example, what types of modifications and what degree of changes can be made to a molecule an have that molecule be considered an analog of the cDNA molecule, rather than a different molecule, for example, does analog include base changes and, if so, how many base changes can be made in the cDNA and still be considered an analog?

Claim 32 recites the limitation "the antisense cDNA's" in line two of the claim. There is insufficient antecedent basis for this limitation in the claim, because it depends from claim 29, which recites one antisense cDNA. Claim 33 is indefinite for the same reasons due to dependence on claim 32.

Claim 32 is indefinite because it is unclear how the method of claim 32 and 29 are related, for example, is the individual recited in claim 32 the mammal recited in claim 29, or are antisense cDNA's administered to two different individuals/mammals. It is unclear if claim 32 is limiting the method of administration of claim 29 or if it is an entirely separate method. Claim 33 is indefinite for the same reasons due to dependence on claim 32.

Claim 34 recites the limitation "said tbdn-1 protein" in line 3 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 35 recites the limitation "said tbdn-1 protein" in line 3 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 41 is indefinite due to the recitation "derived from". The metes and bounds of the term "derived from" are unclear, for example, what types of changes and what degree of changes can occur in a molecule to be considered to be "derived from" SEQ ID NO: 3 or 4, rather than being an entirely different cDNA. Claim 42 is indefinite for the same reasons due to dependence on claim 41.

Claim 46 is indefinite due to the recitation "derived from". The metes and bounds of the term "derived from" are unclear, for example, what types of changes and what degree of changes can occur in a molecule to be considered to be "derived from" SEQ ID NO: 3 or 4, rather than being an entirely different cDNA. Claims 47 and 48 are indefinite for the same reasons due to dependence on claim 46.

Claim 47 is indefinite because the antecedent basis for "the antisense oligonucleotides" is unclear because it depends from claim 46, which recites only one antisense oligonucleotide. Claim 48 is indefinite for the same reasons due to dependence on claim 47.

Claim 47 is further indefinite because it is unclear how the antisense can be phosphoramidate, phosphorothioate, methylphosphonate and other modified analogs. For example, do the antisense oligonucleotides comprise backbone modifications of each type, or do the antisense oligonucleotides comprise all of one type of backbone modification and, if so, are all linkages required to be a particular type or do the claimed antisense oligonucleotides comprise at least one of the recited linkages. Claim 48 is indefinite for the same reasons due to dependence on claim 47.

Claim 47 is indefinite because the scope of "other modified analogs of said cDNA molecules". It is unclear what "analogs" would encompass, for example, what types of modifications and what degree of changes can be made to a molecule an have that molecule be considered an analog of the cDNA molecule, rather than a different molecule, for example, does analog include base changes and, if so, how many base changes can be made in the cDNA and still be considered an analog? Claim 48 is indefinite for the same reasons due to dependence on claim 47.

Claim 48 is indefinite because it is unclear what step claim 48 adds to the methods of claims 46 and 47, because claims 46 and 47 seem to require that the antisense oligonucleotide is generated ex vivo, and then administered to the mammal. It is unclear if claim 48 requires a second antisense oligonucleotide to be generated and administered to the cell or if it is clarifying the method of making the antisense oligonucleotide administered in claims 46 and 47, which seems to be inherent to the methods of claims 46 and 47 and, therefore, claim 48 would not further limit claims 46 and 47.

Claim 49 is indefinite due to the recitation "derived from". The metes and bounds of the term "derived from" are unclear, for example, what types of changes and what degree of changes can occur in a molecule to be considered to be "derived from" SEQ ID NO: 3 or 4, rather than being an entirely different cDNA.

Claim 49 recites the limitation "said condition" in line 5 of the claim. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 2-5, 8, 11-13, 15-17, 19-22, 24-28, 30-35 and 41-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification discloses SEQ ID NO: 2 which corresponds to the cDNA encoding the human species of protein tubedown-1 and further discloses SEQ ID NO: 3 and 4, which consist of antisense sequences which correspond to a sub-sequence of the antisense sequence of SEQ ID NO: 2. SEQ ID NO: 2, 3 and 4 meet the written description provisions of 35 USC 112, first paragraph. However, claims 2-5, 8, 11-13, 15-17, 19-22, 24-28, 30-35 and 41-49 are directed to encompass gene sequences, sequences derived from SEQ ID NO: 2, 3 and 4, corresponding sequences from other species, mutated sequences, sequences which encode a protein with at least 70% homology with SEQ ID NO: 1 and sequences that are at least 70% complementary to SEQ ID NO: 2. None of these sequences meet the written description provision of 35 USC 112, first paragraph. Claim 35 is drawn even more broadly to encompass methods of inhibiting the expression of tubedown-1 using any biological or chemical factors. This broad genus would encompass biological or chemical factors which have absolutely no structural elements in common with the two disclosed antisense molecules, for

example, these biological and chemical factors may not even be nucleic acids. The full genus of biological and chemical factors required for these methods are not described by the instant specification. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO: 2, 3 and 4, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an

> adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.
>
> The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

Therefore, only SEQ ID NO: 2, 3 and 4, but not the full breadth of the claim (or none of the sequences encompassed by the claim) meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Claims 15-33 and 46-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 15-33 and 46-49 are drawn to methods of providing an antisense molecule to cells in vivo (whole organism) using a vector to express the antisense or by administering the antisense to cells, and inhibiting the expression of tubedown-1 protein

and further, wherein a treatment effect for osteosarcoma, including Ewing's sarcoma, is achieved using this antisense.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 15-33 and 46-49 are drawn to methods of treatment and delivery of antisense that require a vector expressing antisense to be delivered to generally any target cell to an organism. The claimed methods of treatment would require that antisense, or a vector expressing antisense, be delivered to a tumor cell at a concentration effective to inhibit the expression of tubedown-1 to a level that would result in a treatment effect for osteosarcoma. The claimed methods of treatment depend on inhibition of tubedown-1 protein expression to realize a treatment effect for osteosarcoma.

The specification has provided examples wherein EWS-96 cells are transfected in vitro with a vector expressing antisense targeted to tubedown-1 and the expression of tubedown-1 is inhibited. The specification has provided examples wherein EWS-96 cells are transfected with a vector expressing antisense targeted to tubedown-1 and these cells are transplanted into immune compromised mice. EWS-96 cells transfected with a vector expressing antisense targeted to tubedown-1 grow more slowly in this

xenograft mouse model relative to EWS-96 cells that do not express tubedown-1 antisense.

The specification does not provide any examples wherein antisense is delivered to cells in vivo (whole organism), nor wherein a vector expressing an antisense targeted to tubedown-1 is delivered to cells in vivo (whole organism). The specification has not provided any examples wherein a treatment effect for osteosarcoma is provided using antisense targeted to tubedown-1. The one example provided using in vivo (whole organism) data does not appear to be relevant to the treatment methods claimed, for example, the specification has not provided any guidance on how to treat osteosarcoma by implanting tumor cells expressing tubedown-1 antisense into an organism.

At the time the instant invention was made, the therapeutic use of antisense oligonucleotides was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of antisense *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, Vol 6, p 72-81, February 2000), Branch (TIBS 23, Feb 1998, p45-50), Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonantisense effects. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery....Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for

therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo*, with a resultant therapeutic outcome, as claimed. The specification provides examples wherein antisense is delivered to cells *in vitro* and the expression of tubedown-1 is inhibited, however, cell culture examples are generally not predictive of *in vivo* inhibition due to differences in metabolites and clearance rates, local concentration of antisense, differences in target site accessibility, cellular uptake differences and the potential for non-antisense side effects. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled *Cellular uptake facilitators for in vitro studies*) states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....In vitro,

cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

The claimed methods are further drawn to methods that require the delivery and expression of a vector expressing an antisense targeted to tubedown-1. These gene therapy methods have additional hurdles in vivo (whole organism). Gene therapy methods are further complicated by problems with low expression, unpredictable loss of expression and unpredictable, possibly lethal, immune responses (see for example, Verma, Anderson). For example, gene therapy methods require expression of the antisense molecule to be high enough, and sustained long enough, to inhibit tubedown-1 such that it results in a therapeutic effect. Treatment methods for osteosarcoma would particularly require sustained expression. Expression of vectors *in vivo* (whole organism) is unpredictable, often too low for therapeutic effects or unexpectedly turned off (see Verma et al., for example). Effective expression requires an appropriate promoter-enhancer combination, "the search for such combinations is a case of trial and error for a given type of cell"(see Verma, for example, p 240). The one example provided by the specification wherein a vector expressing tubedown-1 antisense is used to inhibit the expression of tubedown-1 is wherein the vector is introduced into cells in

vitro and these cells are transplanted into a mouse. This example would not provide any guidance for delivering a vector to osteosarcoma cells in an organism in vitro.

Due to the lack of specific guidance, one skilled in the art would need to practice undue trial and error experimentation to practice the methods of treatment, as claimed, over the full scope claimed. This experimentation would require the determination of how to specifically deliver tubedown-1 antisense, or a vector expressing such, at a concentration effective enough to result in a treatment effect, or, in the case of vector delivered antisense, in a manner that results in high enough expression, or sustained expression, to result in a treatment effect being obtained. This would require the determination of compositions, dosages, routes of administration, regions of the tubedown-1 gene accessible to antisense *in vivo*, and effective promoter-enhancer combinations for expression of tubedown-1 antisense in a particular target cell. Due to the lack of specific guidance in the instant specification, one skilled in the art would need to determine these factors *de novo* and, due to the lack of predictability exhibited for methods of treatment using antisense or gene therapy methods, one skilled in the art would not even predict that this undue experimentation would result in a method which can result in treatment effects for osteosarcoma.

Therefore, due to the broad breadth of the claims, the nature of the invention, the high unpredictability of the art, the lack of sufficient guidance provided by the inventor, the lack of working examples, and the quantity of experimentation required, it would have required undue trial and error experimentation for one skilled in the art to practice the invention as claimed, over the full scope claimed.

***Conclusion***

Claim 1 is allowable as the prior art does not teach or disclose a nucleic acid consisting of SEQ ID NO:1.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Friday 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

PATENT EXAMINER

Karen A. Lacourciere
July 25, 2002